New insights into the autoantibody-mediated mechanisms of autoimmune bullous diseases and urticaria

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Abbreviations: ACE: angiotensin-converting enzyme; auto-Ab: auto-antibody; BMZ: basement membrane zone; BP: bullous pemphigoid; DH: dermatitis herpetiformis; DSG-3, desmoglein 3; IVIG: intravenous immunoglobulin; MMP: mucous membrane pemphigoid; PG: pemphigoid gestationis; PV: pemphigus vulgaris; transglutaminase: TG.

ABSTRACT

The skin is a common target of cellular and/or antibody mediated pathological immune responses. Pemphigoids, pemphigus vulgaris and dermatitis herpetiformis are bullous disease due to autoantibodies targeting specific proteins of the skin. The pemphigoid autoantigens are the BP180 and the BP230 antigens, two components of the epithelial basement membrane zone. Additional antigenic targets reported in a portion of patients are laminin 5, the α6 subunit of the hemidesmosomal integrin α6β4 and a glycoprotein termed p200. The epidermal and mucosal epithelial cells detachment (acantholysis) characteristic of pemphigus vulgaris is induced by autoantibodies directed against the desmoglein 3 and 1. The desmogleins are desmosomal cadherins, which play a major role in the cell-to-cell adhesion. Dermatitis herpetiformis is regarded as cutaneous phenotype of coeliac disease. A novel autoimmune hypothesis of coeliac disease links wheat gliadin and tissue transglutaminase (TG2) in the gut, which leads to T cell response and IgA autoantibody formation. In dermatitis herpetiformis skin the target for IgA deposition seems to be epidermal TG3. Urticaria is a complex syndrome caused by both immune and non-immune mechanisms. In a subsets of patients with chronic urticaria mast cell degranulation is induced by autoantibodies directed against the α-subunit of the high-affinity IgE receptor, and/or the IgE.

Introduction

The skin is the site of diverse autoimmune diseases mediated by auto-antibodies (auto-Abs). These include a number of acquired blistering diseases and a subset of patients with chronic urticaria. Autoimmune bullous disorders comprise the pemphigoid and pemphigus group of disease, secondary to an abnormal auto-Ab response to components of the dermo-epidermal junction or epidermal desmosomes, respectively. These disorders affect typically the elderly, run a chronic-relapsing course, can be severe and may require long-term systemic immunosuppressive therapy. It is therefore, very important an early diagnosis, and the availability of objective criteria to avoid potentially harmful therapy when the disease is under clinical remission. The identification of the target antigens for the auto-Abs has led to the discovery of many components of the desmosome and the adhesion complex linking the epidermis to dermis. In parallel, this work has led to a better understanding on the role of the same proteins in some genetic bullous disease. Dermatitis herpetiformis is now recognized as particular phenotype of celiac disease, where IgA molecules directed against wheat gliadin react with type 3 transglutaminase in the skin. A portion of patients with chronic urticaria have auto-Abs directed against the α-subunit of the high-affinity IgE receptor, and/or the IgE.

Pemphigoid autoantigens and pathophysiology

The epithelial basement membrane zone (BMZ) is the target structure of two groups of severe and even life-threatening blistering disorders, autoimmune sub-epithelial blistering diseases and inherited epidermolysis bullosa. The involved proteins are constituents of the "hemidesmosomal adhesion complex", a functional unit comprising keratin filaments, epithelial adhesion devices named hemidesmosomes and anchoring fibers, that provides stable attachment of basal cells of stratified epithelia to the underlying mesenchyme. Sub-epithelial autoim-

mune bullous disorders presenting with blister formation in the upper zone (lamina lucida) of the BMZ are termed pemphigoids and include bullous pemphigoid (BP), pemphigoid gestationis (PG) and mucous membrane pemphigoid (MMP). BP, the most common subset, presents with generalized skin blisters and usually affects the elderly (1), while PG is characteristically associated with pregnancy. MMP typically affects mucous membranes, prevalently the oral and ocular ones, with occasional involvement of the skin and often leads to scar formation (2).

The hallmark of the pemphigoids is the presence of *in situ* bound and circulating autoAbs (auto-Abs) directed against components of the epithelial BMZ. BP patient IgG auto-Abs target two protein components of hemidesmosomes: the BP180 antigen (or collagen XVII), a type II collagenous transmembrane protein, and the cytoplasmic BP230 antigen. Epitope mapping analyses have shown that auto-Abs are prevalently directed against the membrane-proximal noncollagenous region of the BP180 ectodomain, termed NC16A domain (3), and the C-terminal domain of BP230. Moreover, auto-Abs targeting epitopes distributed over the entire sequence of these antigens have been detected (4). Additional antigenic targets reported in a portion of BP patients are the epithelial adhesion ligand laminin 5, the α6 subunit of the hemidesmosomal integrin α6β4 and a glycoprotein termed p200. PG patient auto-Abs react mainly with the NC16A domain, and also with additional epitopes of BP180 (unpublished observations) and with BP230. The humoral response in the heterogeneous group of MMPs is directed to different antigens, in particular BP180, BP230, α6 and β4 integrins, laminin 5 and 6, and type VII collagen. Several studies have attempted to draw a relation between targeted antigens/epitopes and clinical features or patient subsets. For instance, the ocular form of MMP has been associated with reactivity against the β4 integrin. As to BP patients, significant relationships have been described between i) a more severe phenotype and elevated IgG levels against BP180 ectodomain (5), ii) the presence of both skin and mucosal involvement and reactivity with multiple extracellular epitopes of BP180 (4, 5), iii) focal lesions and reactivity against BP230. In contrast to the extensive data on the humoral response in pemphigoid patients, a very limited number of studies has addressed the role of autoreactive T cells in the pathogenesis of these disorders. Immunogenetic analyses have shown that the presence of DQB1*0301 allele confers a predisposition to BP and MMP and may have a role in T cell recognition of BMZ antigens. It has been recently demonstrated that T cell reactivity targets the same regions of BP180 and BP230 which are also recognized by IgG auto-Abs. Specifically, autoaggressive T cells of BP and PG patients react against the NC16A domain and, in the case of BP, also against the central and C-terminal portion of BP180 ectodomain.

According to the current model of autoimmune disorders, it has been conjectured that auto-Abs against the ectodomain of BP180 have an initiatory role in the development of the disease, whereas the appearance of Abs against the cytoplasmic protein BP230 and the intracellular domain of BP180 represents a secondary event. In keeping with this model, preliminary data from our laboratory show a humoral response initially directed against the BP180 ectodomain, followed by recognition of additional intracellular epitopes. Observations supporting the pathogenic role of auto-Abs to BP180 in BP and PG include: i) the possible occurrence of a transient bullous eruption in the neonate, associated with transplacentar transfer of anti-BP180 auto-Abs from the mother affected by PG, and ii) the correlation between the level of auto-Abs against NC16A and disease activity. To further characterize the role of auto-Abs and to dissect the mechanisms of blister formation in the pemphigoids, *in vivo* and *in vitro* models have been developed. In 1993, Liu and coworkers showed that the passive transfer into neonatal mice of rabbit IgG Abs against murine NC16A induces a blistering disorder mimicking human BP (6). In subsequent studies with genetically engineered mice, the same Authors have provided evidence that subepidermal blister formation is dependent upon complement activation, degranulation of dermal mast cells, and neutrophil recruitment. Neutrophil-derived matrix metalloproteinase 9 inactivates the α1-proteinase inhibitor of neutrophil elastase that in turn induces dermal-epidermal separation by degradation of BP180 (7). Although the auto-Ab reactivity against the cytoplasmic BP230 antigen has been often considered an epiphenomenon, some literature data suggest a role of auto-Abs targeting this antigen in the pathogenesis of BP. In particular, the passive transfer in neonatal mice of Abs against BP230-derived peptides has been reported to induce a dermal inflammatory reaction and subepidermal microdetachments (8).

The failure to reproduce a BP disease by passive transfer of patient auto-Abs into animals has been ascribed to differences in antigen sequences among human and other species or to the need for prolonged antigen/antibody interaction in order to induce disease. Thus, to investigate the pathogenic role of patient sera and the relative contribution of different antigens and/or epitopes, an *in vitro* model based on incubation of human skin cryosections with patient auto-Abs was set up. Auto-Abs specific for NC16A were able to induce a dose-dependent dermal-epidermal separation that appeared to be dependent on the presence of leukocytes. Preadsorption of sera against NC16A completely abolished the blister inducing ability of PG but not of BP sera, suggesting a possible pathogenic role of additional antigens or BP180 epitopes. In the heterogeneous group of MMPs, different antigens appear to be involved in the induction of autoimmune response and blister formation. Concerning the pathogenic role of laminin 5, the passive transfer of specific Abs into neonatal mice induced sub-epidermal blisters in the skin and mucous epithelia, independent of complement activation or degranulation of dermal mast cells and in the absence of inflammatory infiltrate (9). Recently, MMP sera targeting an intracellular domain of β4

integrin were reported to cause dermal-epidermal separation in an organ culture model of oral mucosa (10). The future development of *in vivo* models of active disease for the different pemphigoids appears crucial to dissect the sequence of events that leads to blister formation and to develop novel and more effective therapeutic strategies for these autoimmune disorders.

Protective effect of intravenous immunoglobulin (IVIG) in an experimental model of pemphigus vulgaris

Pemphigus is a group of organ-specific autoimmune mucocutaneous blistering disorders with an established immunological basis. The clinical hallmark of pemphigus is the presence of intraepithelial blisters and erosions of the skin and the mucous membranes. Histologically, cell-to-cell detachment of epidermal and mucosal epithelial cells (acantholysis) caused by IgG Abs directed against desmosomal adhesion molecules characterize pemphigus vulgaris (PV). These Abs can be visualized using the direct immunofluorescent technique (11-13). The pathogenicity of pemphigus Abs was investigated and proved both *in vivo* and in animal models (12-15). The following findings have contributed to the understanding of the pathogenesis: several studies have shown that the severity of the disease correlates with the antibody titer; passive transfer of pemphigus Abs to mice produces acantholysis and intraepidermal detachment. The next step in understanding the pathogenicity is the recognition of the target antigens. The target antigen in PV is a desmosomal protein, namely desmoglein 3 (DSG-3) with a molecular weight of 130 kd. The desmogleins were shown to belong to family of calcium-dependent molecule, called cadhedrins, which play a major role in the cell-to-cell adhesion. The goal of therapy is the elimination or neutralisation of the pathogenic auto-Abs. Currently, there are no really curative treatments for patients that have been diagnosed with PV. PV, left untreated, has a natural history of relentless progression, with 50% mortality at 2 years and almost 100% at 5 years. Since the 1950s, substantial progress has been made in the development of immunomodulatory agents to manage organ transplant rejection, autoimmunity, and inflammatory disorders. The survival of PV patients improved remarkably with the introduction of corticosteroids and other immunosuppressive drugs such as azathioprine, mycophenolate mofetil and cyclophosphamide, the use of which is however limited by numerous and serious side effects. In particular, immunosuppressants weaken the body's defence against other potential pathogens, thereby making the patient more susceptible to infection and other potentially fatal diseases, such as cancer. In some of these instances, the side effects of current treatment modalities can be fatal. Thus, patients with PV need an effective, but more safe treatment.

Intravenous immunoglobulin (IVIG) is a blood product prepared from the serum of thousands donors per batch. In the last decade IVIG has been increasingly used as an immunomodulatory therapy for patients with autoimmune and systemic inflammatory diseases, including PV, systemic lupus erythematosus, dermatopolymyositis, multiple sclerosis, myasthenia gravis, Guillain-Barre syndrome, antiphospholipid syndrome, and more (15-17). The spectrum of antibody specificity expressed in the product is extremely large and IVIG does not only recognize a large number of bacterial, viral and other infectious agents antigens, but also exhibits anti-idiotypic specificity. Therefore, in addition to traditional replacement therapy in immunodeficient conditions, IVIG is currently being used also as immunomodulatory agent in autoimmunity and allogeneic bone marrow transplantation. Despite encouraging reports on the efficacy of IVIG in autoimmune disorders, the clinical efficacy and indication in PV patients remain undetermined. Several studies demonstrate significant effect of IVIG on overall disease activity (19). The beneficial effects are usually prompt, with marked improvement seen within few weeks; however they are of limited duration, with the clinical improvement lasting a few weeks after the last infusion. The clinical response could be maintained by continuous monthly IVIG infusions. Although the first study advocated beneficial effect of IVIG only for acute exacerbation, several later studies have shown significant improvement also in chronic refractory disease. Two uncontrolled studies have so far demonstrated that anti-desmoglein Abs decline significantly during IVIG therapy. However, the clinical efficacy of IVIG and the indications for its use in PV remain unclear, and no controlled double blind or animal studies have been performed.

The aim our study was to investigate the beneficial effect of IVIG using an in-vitro controlled design (20). The ability of IVIG to affect the binding of IgG affinity purified from 2 patients with PV to DSG-3 in comparison to IgG from one donor was conducted by ELISA. We assessed the effect of IVIG on the induction of experimental-PV in CD1 newborn mice by subcutaneous subjection of IgG affinity purified from 2 patients with PV. The treatment was conducted by subcutaneous administration of IVIG together with IgG from the pemphigus patients or appropriate control. The skin of the newborns was examined 24-48 hrs later for blister formation, and samples of the affected areas were analyzed by immunohistochemistry. Our data showed that IVIG as a whole molecule and its F(ab)2 portion, inhibited the binding of anti- DSG-3 antibody to recombinant DSG-3 in a dose dependent manner. The specificity was confirmed by competition assays. *In-vivo*, IVIG and its $F(ab)_2$ portion prevented blister formation in the newborn mice. Cutaneous lesions were noted only in the groups of newborn mice who were injected with IgG fractions from the PV patients. Immunopathological evaluation revealed that IVIG prevented the formation of acanthylosis with IgG deposition in the intercellular spaces. In summary, this study offers strong clinical and immunopathological evidence that IVIG contain anti-anti-DSG-3 activity (anti-DSG-3 anti-idiotypes) capable of neutralizing the binding of PV-IgG to DSG-3. Furthermore, IVIG is a useful agent in the prevention

of blister formation in PV experimental model *in vivo*.

Dermatitis herpetiformis

Dermatitis herpetiformis (DH), described 120 years ago, is a life-long blistering skin disease with predilection sites on elbows, knees and buttocks. The age at onset is mostly 30 - 50 years but it can appear also in childhood or later in life. DH is common in the Nordic countries (prevalence up to 66/100,000), Scotland and Ireland, and about 90% of the patients have HLA-DQ2 (21). The patients have asymptomatic coeliac disease in the small intestine and also the rash responds to a gluten free diet treatment (22). DH is now regarded as cutaneous phenotype of coeliac disease, which in addition to subclinical coeliac disease has pathognomonic IgA deposits in the dermis (21, 23). A novel autoimmune hypothesis of coeliac disease links wheat gliadin and tissue transglutaminase (TG2) in the gut, which leads to T cell response and IgA autoantibody formation (24). In DH skin the target for IgA deposition seems to be epidermal TG3 (25).

A hypothesis of autoimmune pathogenesis of coeliac disease consists of deamidation of wheat gliadin by TG2, its binding to HLA-DQ2^{+} antigen presenting cells and recognition by gut T cells with subsequent production of epithelial damaging cytokines, matrix degrading metalloproteases, and formation of IgA Abs against TG2 (23, 26). These Abs are deposited in the jejunal mucosa but how they are involved in the pathogenesis of villous atrophy is not exactly known. An old hypothesis in DH suggested that clinically silent but immunologically active coeliac disease in the gut could produce IgA Abs which were cross reactive with connective tissue in the skin. Recently, it was found that IgA deposits in DH skin co-localize with TG3 and that circulating IgA TG Abs have higher affinity to TG3 than to TG2 present in the gut and many other tissues (25). DH mouse model failed, however, to confirm that circulating IgA TG Abs are needed for the production of skin lesions (27). An early event in blister formation in DH is accumulation of neutrophils in the papillary dermis. It seems evident that these cells could bind to the deposited IgA and release enzymes and inflammatory mediators causing basement membrane damage and subsequent blister formation (21). It is of interest that dapsone, a drug which controls blistering in DH within a few days suppress effectively superoxide production and release of elastase from the neutrophils (28).

Coeliac disease is well known to cluster in families and, similarly, 18% of the patients with DH were found to have affected first-degree relatives in a recent study in Finland (29). The prevalence among relatives was similar for both diseases; 4.7% and 3.9% of the relatives had coeliac disease and 0.8% and 1.5% had DH, respectively. DH, as coeliac disease, has been found in association with many autoimmune disorders. Autoimmune thyroid disease occurred in 4%, type 1 diabetes in 2.3% and Sjögren´s syndrome in 1% of the Finnish patients with DH (30). There are also reports describing autoimmune liver, kidney and skin diseases such as lupus erythematosus and vitiligo in the patients with DH. The patients with DH, as patients with coeliac disease, have 5-10 times increased risk for lymphoma. In our series, 11 (1%) patients contracted lymphoma 2-31 years after the diagnosis of DH (31). These were mostly B-cell-type lymphoma but two were enteropathy-associated T-cell lymphoma. The DH patients with lymphoma had not adhered as strictly to the gluten-free diet as the control patients without lymphoma. In agreement with this, a previous collaborative study from England and Finland documented that adherence to strict gluten free diet for more than 5 years protects against development of lymphoma (32). The same could be true for the development of associated autoimmune disorders and it is also important that the survival rate of the patients with DH adhering to a gluten free diet is the same or even better than in general population (33).

Urticaria

Urticaria is a vascular reaction of the skin marked by the transient appearance of smooth slightly elevated patches (wheals) that are erythematous and often attended by severe pruritus. Urticaria was named for the stinging nettle plant (Latin Urticaria), which is now recognized to release histamine (34). Angioedema consists of swellings of the deep dermis and subcutaneous or submucosal tissues which last for 24-72 hours. Angioedema may occur alone, but occurs often, along with wheals, in patients with urticaria. Urticaria is a frequent skin condition, with a lifetime prevalence of 15-25% of the general population, and it is more prevalent in middle-aged women. Most cases of urticaria are self-limited and of short duration, but when urticaria becomes chronic, it can be a very problematic and frustrating condition, both for the patient and for the clinician. Chronic urticaria varies in severity, but can cause significant disability. In a recent study, patients with chronic urticaria experienced quality of life impairment similar to that of patients with psoriasis and atopic dermatitis (35). The size, number and shape of the wheals may vary substantially. Larger wheals often tend to heal in the middle and reproduce annular or geographic lesions. The duration of individual wheals is typically less than 24 hours. Lesions that last more than 24 hours, are painful (more than pruritic), leave permanent pigmentary change, show the presence of vescicles, or are accompanied by purpura suggest urticaria vasculitis.

Urticaria is defined as either acute or chronic if present for less or longer than 6 weeks, respectively. A recent, clinically oriented, classification of urticaria distinguish four different groups (36): i) spontaneous urticaria, comprising acute and chronic urticaria; ii) physical urticaria, including dermographic, delayed, cold contact, heat contact, solar and vibratory urticaria; iii) special types of urticaria, including cholinergic, adrenergic, contact and aquagenic urticaria; iv) different diseases (not urticaria) traditionally related to urticaria, encompassing urticaria pigmentosa, urticaria vasculitis etc. Acute urticaria represents the most frequent type of urticaria. Potential causes of acute urticaria

include drugs (penicillins, cephalosporins, salicylates, nonsteroidal anti-inflammatory drugs, barbiturates, amphetamines, atropine, hydralazine, insulin, blood, and blood products, angiotensin-converting enzyme [ACE] inhibitors and opiates), foods (tree nuts, peanuts, eggs, shellfish, tomatoes, aged cheeses, or red wine), infections (Epstein-Barr virus; hepatitis, A, B, and C; adenovirus; enterovirus; *Helicobacter pylori* and parasites) and inhalants (latex and flour). Chronic urticaria recognizes a wide number of causes, but the number of patients in which aetiology can be established appears to be a minority. There are several reports dealing with those causes, including food allergies, pseudoallergic reactions against food and food additives, internal diseases (thyroid diseases, connective tissue diseases and paraproteinemia), viral or bacterial (e.g. *H. pylori*) infections. The role of foods and food additives remain controversial because only in a minority of patients urticaria has been reproduced in double-blind placebo-controlled oral challenge test (36). Also the role of infectious agents is still disputable. A recent review excluded an increased prevalence of infections (including *H. pylori*) among patients with chronic urticaria (37). Only parasites are recognized as a cause, although rare, of chronic urticaria. There is a lack of association between chronic urticaria and cancer. AutoAbs to thyroid (thyreoglobulin and thyroid peroxidase) are elevated in 5-34% of patients with chronic urticaria (38).

In a subset of patients affected by chronic urticaria (at least 30%), mast cell and basophil-degranulating serum Abs have been isolated. Those are mainly Abs to the alpha subunit of the high-affinity IgE receptor, and less frequently to IgE (39). Complement appears to be required for histamine release by these auto-Abs, C5a being the critical component (40). Evidence suggests that such Abs are functional *in vivo*, but conclusive data are still lacking. Physical urticaria are induced by different specific external physical stimuli, such as mechanical forces (dermographic if the pressure force is applied tangentially to the skin; delayed-pressure urticaria if the pressure force acts perpendicular to the surface of the skin), heat, cold, sunlight, vibration. The prognosis for chronic urticaria is relatively good: spontaneous resolution occurs within 12 months in 50% of patients. Patients with auto-Abs tend to have a worse disease and physical urticaria tend to run a longer course. The diagnosis of urticaria is primarily clinical and it is very important to spend time documenting clinical details. Intradermal injection of autologous serum offers a surrogate test for screening patients for auto-Abs. Treatment of urticaria includes avoidance of triggers, when known, and pharmacotherapy. In general, patients should avoid drugs known to either cause or exacerbate hives, such as non-steroid antiinflammatory drugs, opiates, and ACE inhibitors. Acetaminophen may be a substitute treatment to control pain. ACE inhibitors should be discontinued in anyone experiencing angioedema. If physical urticaria is present then relevant physical factors should be avoided whenever possible.

Histamine H1 receptor antagonist are the mainstay in the treatment of urticaria. Newer-generation H1 antihistamines (acrivastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine and mizolastine) are generally quite effective in controlling the condition and have a better safety profile. First-generation antihistamines, such as hydroxyzine, diphenhydramine hydrochloride, and cyproheptadine hydrochloride, may be an add-on therapy. Taking antihistamines according to a schedule rather than on an as-needed basis is the key to attaining disease control. Doses may need to be adjusted upward, depending on the severity of the disease. Continuing research on the exact mechanism of H1 antihistamines has revealed that the use of term "receptor antagonist" may be a misnomer, because all present H1 antihistamines probably function as inverse agonists, stabilizing the receptor in an inactive conformation. This finding may account for the clinical observation that H1 antihistamines work better when taken prophylactically and are distinctly less effective after histamine has been released and is bound to the receptor. If symptoms are not optimally controlled with H1 antihistamines, addition of an H2 blocker should be considered. Leukotriene receptor blockers used as add-on therapy to H1 antihistamines have been shown to provide some benefit in some studies but not in others. Short course of corticosteroids are useful in patients with more severe disease. In patients with severe and refractory urticaria, cyclosporine, intravenous immunoglobulin, plasmapheresis, methotrexate, colchicine, dapsone, sulfasalazine, hydroxychloroquine sulfate and warfarin sodium have been employed.

Concluding remarks

There is a wide variety of auto-Ab-mediated skin diseases. The discovery of the autoimmune origin of these diseases and the characterization of structure and function of the target antigen have greatly increased our understanding of skin physiology. The auto-Abs detection systems have greatly improved for an earlier and more precise diagnosis. On the other hand, this progress appears essential for developing novel and more effective therapeutic strategies for these disorders.

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